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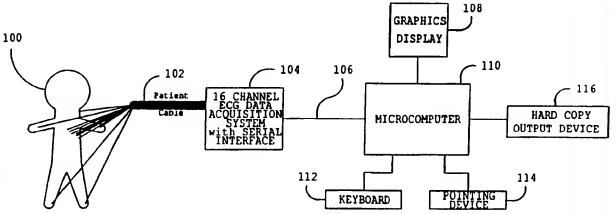

(57) Abstract

Patient leads (101) are connected to a patient (100) and ECG signals are picked up by the leads and transmitted over a patient cable (102) to a 16-channel ECG data acquisition system (104) with a serial interface. The data acquisition system (104) filters, amplifies and digitizes the ECG waveforms and sends the digitized data to a microcomputer (110) via a high speed synchronous serial line (106). The microcomputer (110) processes the serial data stream in order to generate computed data arrays. These arrays are then used in conjunction with predetermined reference arrays to produce diagnostic indices. These indices are displayed on the graphics display (108). Printed output is available on the hard copy output device (116) which is connected to the microcomputer (110). Interaction between the operator and the system is provided by means of a keyboard (112) and pointing device (114) with feedback on the graphics display (108).

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CARDIAC BIOPOTENTIAL ANALYSIS SYSTEM AND METHOD

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part application of co-pending United States Serial No. 107,419 filed October 9, 1987, which is also assigned to the assignee of the present application

BACKGROUND OF THE INVENTION

The present invention relates to a high-frequency, high-resolution cardiac biopotential analysis apparatus and method, and more particularly to a microcomputer-based cardiac biopotential analysis apparatus for quantitatively determining in a noninvasive manner, cardiac phenomena that can be ascertained by analyzing cardiac electrical activity.

Cardiac biopotentials arise from the discharge of hundreds of thousands of electrically active cells. The signal detected at the body surface is a composite determined by different types of tissue, differing locations of that tissue, and the type of organization (or disorganization) of the wavefront of activation. When transmitted to the body surface the signal is altered in morphology and frequency content as a result of such factors as body fat, ribcage size, and position of the heart in relation to the lungs. All these variables lead to challenging signal processing problems.

Despite nearly a century of use, the conventional scalar electrocardiogram ("ECG") has major shortcomings. Its value for the diagnosis of coronary artery disease (CAD) is limited. It is very useful when there has been an

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antecedent myocardial infarct (MI) ("heart attack") which leads to localized fibrosis extensive enough to be detectable. In the absence of previous MI, the abnormalities induced by CAD in the resting ECG in an asymptomatic individual are of limited sensitivity and specificity.

The scalar ECG is of much greater value for the detection of active, ongoing ischemia. Monitoring of the ST segment during chest pain is a reliable indicator of cardiac ischemia and is used diagnostically when chest pain spontaneously presents itself or when chest pain is deliberately provoked for diagnostic purposes as in exercise stress testing. However even for this diagnostic application there occur significant numbers of false positives often requiring further, more expensive noninvasive tests (nuclear imaging) or invasive assessment through the use of cardiac catheterization and coronary angiography.

For the assessment of the risk of sudden cardiac death due to malignant ventricular arrhythmias the conventional ECG is of practically no use whatsoever. Twenty four hour continuous ambulatory monitoring of the scalar ECG ("Holter monitoring") is of some value in the minority of individuals with significant amounts of ventricular extrasystoles, but at considerable expense and inconvenience to the patient.

Advances in computer technology have led to attempts to improve the diagnostic information extracted from the surface ECG. One such approach is the cardiointegram (CIG) which has been used for the detection of coronary disease. This approach, as described in "The Cardiointegram: Detection of Coronary Artery Disease in Males with Chest

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Pain and a Normal Resting Electrocardiogram", J. Electrocardiography. 19(3): pp. 257-267 (1986), applies a process of integration over the various sections of the QRST signal thereby highlighting information about the interrelationships of positive to negative deflections from the QRS to the QT interval and T wave amplitude. Using this technique it has been shown that coronary artery disease can be detected from the resting, normal ECG with a sensitivity and specificity slightly less than exercise stress electrocardiography.

More recently Abboud et. al in "High Frequency Electrocardiography Using an Advanced Method of Signal Averaging for Non-Invasive Detection of Coronary Artery Disease in Patients with Normal Conventional Electrocardiogram", J. Electrocardiography. 19(4): pp. 371-380 (1986) showed that high frequency components of the ECG (150-250 Hz) averaged in the frequency domain after fast-Fourier transform exhibited a characteristic "zone of reduced amplitude" in patients with CAD. The sensitivity of this technique was 75%. CIG had similar sensitivity.

A second area in which new computer based techniques have been applied to electrocardiography is in the detection of patients at risk for malignant ventricular arrhythmias and sudden cardiac death. Simson in "Use of Signals in the Terminal QRS Complex to Identify Patients with Ventricular Tachycardia After Myocardial Infarction", Circulation. 64(2): pp. 235-242 (1981) showed that signal averaging in the time domain reveals the presence of low amplitude high frequency deflections in the terminal portion of the QRS complex, so-called "late potentials". These late potentials have been correlated with inducibility of serious arrhythmias in the electrophysiology (EP) lab and with an increased risk of

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sudden death during longterm follow up of survivors of heart attack. However, the detection of late potentials has a poor predictive accuracy due to the problem of false positive tests.

An alternative approach to the detection of risk for arrhythmia uses indices of the power spectrum of the signal averaged QRS. Cain et al in "Fast-Fourier Transform Analysis of Signal-Averaged Electrocardiograms for Identification of Patients Prone to Sustained Ventricular Tachycardia", Circulation. 69(4): pp. 711-720 (1984) showed that this approach can distinguish arrhythmia patients from controls and correlates with inducibility of arrhythmias in the EP lab. Recent attempts to reproduce such results have met with varied success, due to fundamental problems in defining length of segment for FFT and in distinguishing the end of the QRS from noise. Haberl et. al in "Comparison of Frequency and Time Domain Analysis of Signal Averaged Electrocardiogram in Patients with Ventricular Tachycardia and Coronary Artery Disease: Methodologic Validation and Clinical Relevance. JACC. 12(1): pp. 150-158 (1988) applied successive FFTs that are shifted in time to the terminal portion of the signal averaged QRS to address some of the problems with the Cain method. Neither the time-domain indices of "late potentials" nor the power spectral indices of Cain or Haberl have been shown to be influenced by drugs. This has limited the application of these technologies to diagnostics, where the problem of false positives leads to their use as additional procedures at additional cost. Judgement of therapeutic efficacy continues to require additional costly invasive and noninvasive procedures.

The fundamental limitation of techniques applied to the ECG to date is their linear nature. The cardiac

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electrical signal is a complex summary of spatial and temporal inputs and many nonlinear dynamic features should be expected. In particular, neural inputs to the heart will have significant nonlinearities. What is true in health is at least equally true in disease. Thus a disease process can be expected to lead to characteristic alterations in nonlinear properties as well as linear ones. An ability to quantify abnormalities in nonlinear dynamics would therefore be expected to enhance diagnostic power and improve the assessment of therapeutic efficacy.

It is therefore a principal object of the present invention to provide a noninvasive system and method for reliably determining myocardial physiologic properties.

Another object of the present invention is to provide a noninvasive system and method for quantifying linear and nonlinear properties of phase and energy components within the frequency structure of the electrocardiogram.

A further object of the present invention is to provide a noninvasive system and method for diagnosing and quantifying coronary artery disease.

Another object of the present invention is to provide a noninvasive system and method for the detection and quantification of myocardial ischemia in real time, for example as a part of intraoperative monitoring.

Another object of the present invention is to provide a noninvasive system and method for the detection of successful reperfusion of the infarct-related artery in patients given thrombolytic therapy for acute myocardial infarction.

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A further object of the present invention is to provide a noninvasive system and method for the assessment of coronary artery restenosis after successful percutaneous transluminal coronary angioplasty.

A further object of the present invention is to provide a noninvasive system and method for the quantification of cardiac electrical stability fixed or real time and the propensity for arrhythmias whether due to drugs, heart disease, or neural factors.

A further object of the present invention is to provide a noninvasive system and method for the quantification of the extent of malignancy of cardiac arrhythmias.

A further object of the present invention is to provide a noninvasive system and method for the identification of wide-complex supraventricular tachycardia from sustained ventricular tachycardia.

A further object of the present invention is to provide a noninvasive system and method for assessing the efficacy of therapy for arrhythmias and sudden cardiac death whether that therapy is drugs or surgery.

A further object of the present invention is to provide a noninvasive system and method for quantifying the effects of neural and humoral inputs to the heart, including the sympathetic and parasympathetic systems.

A further object of the present invention is to provide a noninvasive system and method for evaluating pump function and quantifying ejection fraction.

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It is still another object of the present invention to provide a noninvasive system and method for quantifying the effects of ongoing organ rejection in cardiac transplant patients.

SUMMARY OF THE INVENTION

The cardiac biopotential analysis system and method of the present invention detects and quantifies the linear and nonlinear dynamic properties of cardiac depolarization and repolarization in a noninvasive manner. In so doing the invention provides a method for quantifying abnormalities in nonlinear dynamics and thereby enables without limitation the detection and quantification of coronary artery disease (CAD), myocardial ischemia, cardiac electrical stability, risk of malignant ventricular arrhythmia, site(s) of origin of malignant arrhythmias, extent of malignancy of arrhythmias, degree of antiarrhythmic drug efficacy, neural and humoral inputs to the heart, pump function/ ejection fraction, and ongoing organ rejection in cardiac transplant patients.

A suitable electrode and amplifier system are used to acquire the cardiac electrical signal from the body surface of a region of interest. Very high frequency content is preserved by setting band pass filters at 0.05-512 Hz. Digital sampling is performed and digitized data is transmitted over a high speed serial line to a host microcomputer. A sinus QRST complex or a ventricular ectopic beat is chosen interactively as a template. Using standard crosscorrelation techniques a preselected number of complexes which match the template are extracted. Autobispectral or crossbispectral analysis is then performed using either an FFT approach or a parametric approach.

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In autobispectral analysis a complex autotriple product array and a real autotriple product array is produced for a number of beats that match the preselected template. All of the autobispectral complex triple product arrays are then added point by point and divided by the total number of beats to create an average autobispectral complex triple product array. The autobispectral real triple product arrays are averaged in the same manner to create an average real triple product array. The magnitude of each averaged point in the complex autotriple product array is then divided by the square root of the real triple product array to form an autobicoherence array. An autobiphase array can also be produced by deriving the arc tangent of the ratio of the imaginary to real part of the complex autotriple product array.

In crossbispectral analysis a complex crosstriple product array and a real crosstriple product array is produced for a number of successive pairs of beats that match the preselected template. After averaging, the resultant average complex crosstriple product array and average real crosstriple product array are used to produce the crossbispectral density array, the crossbicoherence array and the crossbiphase array.

Each of the generated bispectral arrays can contain up to (nfft/2+2)*nfft/8 data points if a nfft-point FFT is used. Although all, or nearly all of the values at these points can be expected to change from normal due to different interventions, drugs, or disease states, in the preferred embodiment only those points which show the greatest fidelity for tracking the diagnostic determination in question are utilized to create a diagnostic criterion. In the preferred embodiment the ensemble of points most

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sensitive to a particular intervention or physiologic process is used to create one or more clinically useful single value indices from the computed bispectral arrays. The indices are then used as diagnostic figures of merit for detection and quantification of coronary artery disease (CAD), myocardial ischemia, cardiac electrical stability, risk of malignant ventricular arrhythmia, site(s) of origin of malignant arrhythmias, extent of malignancy of arrhythmias, degree of antiarrhythmic drug efficacy, neural and humoral inputs to the heart, pump function/ ejection fraction, and ongoing organ rejection in cardiac transplant patients. This approach makes it possible for any, even unskilled, operator to meaningfully interpret the output of the diagnostic device.

In situations where continuous monitoring is required, indices are continuously displayed on a video terminal enabling an operator to interactively evaluate regions of interest. For record keeping purposes index values and other pertinent variables can be sent to a hard copy output device or stored to magnetic storage device, such as a disk.

These and other objects and features of the present invention will be more fully understood from the following detailed description which should be read in light of the accompanying drawings in which corresponding reference numerals refer to corresponding parts throughout the several views.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic diagram of the components of the cardiac biopotential analysis system of the present invention;

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Fig. 2 is a schematic diagram of the 16 channel ECG data acquisition system, utilizing a serial interface, of the cardiac biopotential analysis system as shown in Fig. 1;

Fig. 3 is a schematic diagram of the microcomputer utilized by the cardiac biopotential analysis system of Fig. 1;

Fig. 4 is a block diagram of the interaction of the various tasks performed by the system and method of the present invention;

Fig. 5 is an overview flow chart of the operation of the system and method of the present invention;

Fig. 6 is a representation of the output provided by the system and method of the present invention;

Fig. 7 is a flow chart of the process utilized by the system and method of the present invention for the acquisition of ECG data;

Fig. 8(a) is a diagram of a sample PQRST complex utilized by the system and method of the present invention;

Figs. 8(b) - 8(d) are diagrams of possible extraction templates utilized for bispectral analysis by the method and system of the present invention;

Fig. 9 is a flow chart of the frequency domain based steps for producing the autobispectrum or the crossbispectrum used by the system and method of the present;

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Fig. 10 is a flow chart of the parametric based steps for producing the autobispectrum or the crossbispectrum used by the system and method of the present invention;

Fig. 11 are sample diagrams of autobispectral arrays of the QRS complex generated by the system and method of the present invention;

Fig. 12 is a flow chart of the steps used to generate diagnostic indices by the system and method of the present invention;

Fig. 13 are diagrams of several autobicoherence arrays developed during the determination of the clinical reference arrays;

Figs. 14(a) - 14(b) are tables of the sample indices for normal subjects and for CAD subjects, respectively, generated by the system and method of the present invention in connection with the establishment of clinical reference arrays;

Fig. 15 are diagrams showing sample bicoherence values when the system and method of the present invention is used to identify patients at risk of malignant arrhythmias;

Figs. 16(a) - 16(b) are tables of sample indices for MI subjects and VT/VF subjects respectively;

Figs. 17(a) - 17(b) are graphs of coefficients generated by the system and method of the present invention.

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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring to Fig. 1, the apparatus of the present invention is connected to a patient 100 through a set of surface electrodes using a standard limb, precordial and orthogonal placement protocol. The ECG signals are picked up by the electrodes and transmitted over a patient cable 102 to a 16 channel ECG data acquisition system 104 with a serial interface.

The data acquisition system 104 filters, amplifies and digitizes the ECG waveforms and sends the digitized data to a microcomputer 110 via a high speed synchronous serial line 106. In addition, the serial line 106 can be used to download filtering, gain and sampling rate instructions to the data acquisition unit 104.

The microcomputer 110 processes the serial data stream in order to generate all computed data arrays. These arrays are then used in conjunction with predetermined reference arrays derived from clinical studies to produce diagnostic indices which indicate the status of the patient. These indices are displayed on the graphics display 108. Printed output of the diagnostic index is also available on the hard copy output device 116 which is connected to the microcomputer 110. Interaction between the operator and the system is provided by means of a keyboard 112 and pointing device 114 with feedback on the graphics display 108.

The 16 channel data acquisition system 110 is shown in greater detail in Fig. 2. The ECG surface potential, detected by a surface electrode mounted on the patient 100, passes through an electrosurgery protection circuit 202, a defibrillator protection circuit 206 and an amplifier/

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filter circuit 208 before being passed on to the multi-channel analog to digital converter 210.

The electrosurgery protection circuit 202 includes a radio frequency (rf) filter, which limits the rf current through the patient leads 101 to less than 100 micro amperes and thus protects the patient 100 from rf burns and protects the amplifiers 36 from damage resulting from exceeding the absolute maximum input voltage specified by the manufacturer. This circuit can be an LC section circuit consisting of a generic inductor connected in series to a generic capacitor which is then connected to ground.

The defibrillator protection circuit 206 limits the voltage to the amplifiers 208 to a safe level when a defibrillator is applied to the patient 100 and discharged. This circuit preferably includes a neon light bulb and/or a parallel variable resistor connected in series to a grounded resistor.

The amplifier/ filter circuitry 208 is controlled by a microprocessor 216 for default gain and filtering levels or alternate gain and filtering levels as requested by the operator. Preferred gain and filtering settings are discussed below. This circuitry 208 includes three stages: the first is a pre-amplifier stage that can be assembled using a wide variety of high impedance pre-amplifiers such as those sold by National Semiconductor, Sunnyvale California; the second is a programmable filters stage which can utilize filters sold by Frequency Devices, Haverhill Massachusetts; the third stage is a programmable amplifiers stage which can be assembled from operational amplifiers used in conjunction with a multiplying digital to analog (D/A) converter, both of which components are

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available from National Semiconductor. The multiplying D/A is used to set the gain to the appropriate levels requested by the microprocessor 216.

The high impedance pre-amplifier of each channel will saturate to either the positive or negative supply voltage if the input of the pre-amplifier is not terminated. This will lead to large positive value or a large negative value at the output of amplifier section 208. Such values will be used to identify lead failure.

The output of all 16 channels of the amplifier/ filter 208 is fed to a multi-channel analog to digital converter (A/D) 210 which is under microprocessor 216 control for sampling rate settings. The analog signals are converted to digital data format suitable for input to a computer. A/D converters sold by Analog Devices, Norwood, Massachusetts can be used for this purpose.

The multi-channel A/D converter 210 is optically coupled to data bus 215 by optical isolator 214. All control lines to the amplifiers/ filters 208 and the A/D convertor 210 are also optically isolated by optical isolator 212. Any known optical isolators can be used for this purpose.

All DC power lines going to the amplifiers/ filters 208 and A/D convertor 210 are also isolated from the AC power line with a DC/DC convertor 204 in order to provide complete patient isolation from ground. DC/DC converters available from Burr Brown can be used for this purpose.

The basic instructions for controlling operation of the microprocessor 216 are stored in a read only memory (ROM) 218. The random access memory (RAM) 219 is used as a

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buffer memory for data, and a portion of the RAM 219 can also be used as program memory when a control program is being downloaded from the microcomputer 110.

Serial interface 220 operates under the control of the microprocessor 216. The serial interface 220 is optically coupled with optical isolators 222 to high speed synchronous serial drivers 224 to provide a synchronous serial link 106 between the 16 channel data acquisition system 104 and any compatible high speed synchronous serial interface card on any computer. The serial lines are isolated by optical isolators 222 and DC/DC convertor 204 to provide increased patient safety and to protect the host computer 110 from any transients.

The host or microcomputer 110 of Fig. 1 is shown in greater detail in Fig. 3. The entire microcomputer system runs under control of a microprocessor 302 with the program memory for the microprocessor being stored in ROM 304. The RAM 306 is used for storage of intermediate data. The mass storage device 308 is used for storing clinical databases as well as archiving patient data.

In a preferred embodiment, the microcomputer 110 contains an array processor 310 (such as the Vortex sold by SKY of Lowell, MA) on which complex arithmetic calculations can be performed on entire arrays of data simultaneously. The preferred embodiment also includes a math coprocessor 312 which is connected directly to microprocessor 302. The math coprocessor 312 is used for scalar and graphic calculations while the array processor 310 is used to calculate bispectral and other data vectors.

A graphics controller 314 operating under program control of the microprocessor 302 drives a graphics display

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316. A keyboard controller 318 interfaces directly with the operator's keyboard 320. An interface port 322 is provided for the pointing device 324.

Operator control of the entire acquisition, analysis and display procedure is controlled from the keyboard 320 and pointing device 324 with feedback on the graphics display 316. One high speed synchronous serial port 326 is provided to interface with the 16 channel data acquisition system 104. Port 326 can be used to send control data to the system (e.g., filtering, gain, sampling rate, start/ stop acquisition, perform self diagnostics) and to receive ECG data from the system, as well as to download program data to the system. Another serial or parallel interface port 328 is provided to drive a hard copy output device 330 for printing desired diagnostic indices.

Referring now to Fig. 4, the functions performed by the system and method of the present invention will now be described. As mentioned above, the system and method of the present invention quantify linear and nonlinear properties of phase and energy components within the frequency structure of the ECG from a preselected number of leads. Diagnostic indices are then generated from the bispectral data arrays by utilizing predetermined reference arrays. The indices are used for the quantification of coronary artery disease (CAD), myocardial ischemia, cardiac electrical stability, risk of malignant ventricular arrhythmia, site(s) of origin of malignant arrhythmias, extent of malignancy of arrhythmias, degree of antiarrhythmic drug efficacy, neural and humoral inputs to the heart, pump function/ ejection fraction, and ongoing organ rejection in cardiac transplant patients.

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The monitor module 402, handles the overall operations of the system via integration of data and process information from the user interface module 404, acquisition and raw ECG data management module 406, bispectral processing module 408 and diagnostic index derivation module 410. A detailed description of the operation of module 402 will be provided below in connection with the description of Fig. 5.

The user interface and display management module 404 represents the means through which the operator controls and interacts with the system during the course of a procedure. This includes, but is not limited to, entry of information regarding the patient, type of diagnostic procedure being carried out, lead and acquisition settings; continuous display of acquisition status, lead integrity, display of diagnostic indices; and requests for printing and archiving results to disk. Module 404 directly interacts with the monitor module 402. The operations handled by module 404 can be achieved under one of many commercially available environments such as Microsoft's Windows.

The acquisition and raw ECG data management module 406, handles all of the raw ECG data checking and processing prior to bispectral analysis. This includes, but is not limited to, continuous acquisition of ECG data and the verification of the integrity of the data; performing QRS detection; performing crosscorrelation with the preselected template to identify suitable complexes; extracting suitable complexes from leads of interest in preparation for autobispectral and crossbispectral processing. Module 406 directly interacts with the monitor module 402, and a more detailed description of module 406

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will be provided below in connection with the description of Fig. 7.

The bispectral processing module 408 controls the generation of all data arrays measuring dynamic phase and energy properties within the ECG. This information can be organized in both autobispectral and crossbispectral arrays utilizing either an FFT based or parametric based approach. The tasks include, but are not limited to, nonlinear/ exponential transform of the signal, Fourier transformation, the generation of power spectrum, autobispectral density, crossbispectral density, autobicoherence, crossbicoherence, autobiphase, and crossbiphase. Module 408 directly interacts with the monitor module 402, and a more detailed description of module 408 is provided below in connection with Figs. 9 and 10.

The diagnostic index derivation module 410 generates the data values utilized in the diagnostic process. The task includes, but is not limited to, identifying frequency pairs of interest through the use of predetermined clinical reference arrays and creating a diagnostic index from the values in the bispectral data arrays at the frequency locations defined by the reference array. Module 410 directly interacts with the monitor module 402, and a more detailed description of module 410 is provided below in connection with Fig. 12.

Referring to Fig. 5, the operation of the monitor module 402 will now be discussed. In step 502, the data arrays used to store the digitized raw ECG and the bispectral data of each lead are initialized. The data files required for storage and files containing databases

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required for the computation of diagnostic indices are also opened in the initializing step 502.

In step 504 the system requests the information required to start the acquisition and diagnostic process from the user via the user interface module. This information includes the type of diagnostic procedure to be conducted and any operator requested modification to the system defaults such as leads used, clinical databases to access for diagnostic index computation, filtering, gain and sampling rate information for each lead. The type of diagnostic procedure as entered by the operator will be used by the system to inform the operator of the lead placement protocol required, and the type of template to be selected (sinus rhythm or ectopic beat). The system will also use the type of diagnostic procedure it will perform to select the portion of the complexes to be used as time series for bispectral processing as well the type of bispectral arrays that need to be computed for use in conjunction with the predetermined clinical databases to yield a final diagnosis. The process of identifying the most effective leads for a particular diagnostic procedure and the generation of the clinical databases will be discussed later.

In step 506, ECG signals are continuously acquired and displayed from the leads needed for the diagnostic operation being performed. All channels transmitting artifactual data are properly signaled to the operator to correct the problem. While using the pointing device, the operator is requested to select a suitable template against which incoming ECG complexes are matched.

The system, in step 508, computes the necessary autobispectral and crossbispectral arrays required by the

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databases for the generation of the diagnostic indices requested by the operator.

In step 510, the diagnostic indices from all generated autobispectral and crossbispectral arrays are computed. Autobispectral density and crossbispectral density clinical reference arrays are utilized in these diagnostic index computations. In the case of a static one time diagnostic determination, such as detection of CAD, the system displays, in step 512, the resultant diagnostic indices and a projected outcome based on information from the clinical databases. In the case of monitoring an ongoing cardiac process such as intraoperative ischemia the index is displayed continuously over time during the course of the procedure requiring it.

In step 514, requested printouts are produced, results are stored to disk for archival purposes and all files are closed. In step 516, the process is terminated.

A sample display representation generated by the system is shown in Fig. 6. The top section of the screen 602 is divided into 16 sections 603 each representing the region probed by an electrode. Each section will be covered by a large "X" 604 if lead fail or artifact was detected from the lead corresponding to that section.

A second portion of the screen 606 can be assigned to the continuous display of the diagnostic index if the system is being used in monitoring mode. The background of that portion is color coded to reflect the possible values allowed for in the range of the selected diagnostic index. The most current value of the diagnostic index will dictate what color is displayed in the background (e.g. Red = lowest value to Green = highest value). This will

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facilitate the examination of the patient's status at a distance.

A third portion of the screen 608 can be assigned to displaying one or several of the raw ECG data leads that is being acquired for processing. This will also provide for easy template selection using the pointing device.

A fourth portion of the screen 610 can be assigned to displaying the results of a static diagnostic test if the system is being used in that mode of operation.

Referring to Fig. 7, the acquisition and raw ECG data management module 406 will now be described in greater detail. In step 702, the acquisition system 104 is programed with requested filtering, gain, sampling rate, and lead selection information.

In step 704, the acquisition system 104 acquires continuous ECG data for all requested leads and transfers this data to the host computer 110. The acquisition system 104 detects lead failures during the acquisition cycle, and in step 706, the acquired data is examined for lead failure signals and for the presence of artifact. In step 708, leads generating fail signals and/ or artifactual data are marked for the monitor module 402.

In step 710, the system requests the operator to identify a template from the incoming data stream using the pointing device. In step 712, QRS detection is performed on the ECG data using any publicly available QRS detection program such as the algorithm disclosed by Engelese et al in "A Single Scan Algorithm for QRS-Detection and Feature Extraction", IEEE Computers in Cardiology (1979). Then in step 714, the system initiates continuous extraction of

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complexes that match the template from the incoming ECG data from each lead using standard cross-correlation techniques.

Depending on the diagnostic test requested by the operator and based on information from the clinical databases, bispectral processing will be performed on the full complex that matches the template or a portion of that complex. Also, depending on the test to be performed the complex can be a sinus rhythm beat or an ectopic beat. In step 716, the auto/cross bispectral time records are continuously generated by extracting a portion suitable for the diagnostic test from each matched complex from each of the leads required for the test. Each portion is assigned to an $X_i(t)$, where $X_i(t)$ are the individual time series records provided for autobispectral processing. Also in step 716, $Y_i(t)$ is set to $X_{i+1}(t)$ (the successive complex in the same lead) where $Y_i(t)$ are the time series records (in addition to $X_i(t)$) required for crossbispectral processing within the same lead. $Y_i(t)$ can also assume the value of a corresponding $X_i(t)$ from another lead providing for crossbispectral analysis between two leads. It should be noted that for autobispectral analysis $Y_i(t)$ is set to equal $X_i(t)$ and in all cases the index i denotes the record number from 1 to k, and where k is the number of bispectral averages computed.

Once the acquisition process is initiated the program will continuously pass to the monitor module (via interrupt handlers) raw time series data until the diagnostic test is completed. The program returns control to the monitor module 402 in step 718.

Now turning to Fig. 8, Fig. 8(a) shows a sample PQRST template; Fig. 8(b) shows the QRST portion extracted for

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processing; Fig. 8(c) shows the terminal part of the QRS extracted for processing; and Fig. 8(d) shows the ST segment with the T wave extracted for processing. The axes in Figs. 8(a) - 8(d) are not calibrated and the figures are for illustration purposes only.

Referring now to Fig. 9, the frequency domain based procedures for producing the autobispectrum or the crossbispectrum will now be discussed. In step 902, the system checks whether the computation to be performed is an autobispectral or crossbispectral computation. Autobispectral analysis is a special case of crossbispectral analysis and therefore different rules of symmetry apply.

In step 904, the system sets the following symmetries in order to proceed with autobispectral computation:

$$f_1 + f_2 < N/2$$

where N is the number of samples in the time series to be processed. N will depend on the length of the portion of the complex (in msec) and the sampling rate. For illustration purposes we will utilize the QRS portion of the selected complex with length of 160 msec. Since the sampling rate is 1024 samples/sec N will be equal to 160 samples or 1024 Hz.

$$0 < f_2 < f_1$$

$$X_i(t) = Y_i(t) \text{ ---> } X_i(f) = Y_i(f)$$

where f_1 and f_2 (also referred to as F_1 and F_2 or Frequency 1 and Frequency 2) denote the frequency pairs over which

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bispectral computation will be carried out, $X_i(t)$ and $Y_i(t)$ denote the individual time series records used for bispectral computation, $X_i(f)$ and $Y_i(f)$ denote the Fourier transform of the time series records and i denotes the record number which in this embodiment ranges from 1 to k.

In step 906, the following symmetries are adhered to for crossbispectral analysis:

$$f_1 + f_2 < N/2$$

$$0 < f_1 < N/2$$

$$0 < f_2 < N/2$$

$$-2f_2 < f_1$$

$$X_i(t) \neq Y_i(t) \text{ ---> } X_i(f) \neq Y_i(f)$$

where all variables represent the same values as they do for autobispectral analysis, except that for crossbispectral analysis $X_i(t)$ and $Y_i(t)$ represent individually derived time series records where $Y_i(t) = X_{i+1}(t)$ from the same lead for same lead crossbispectral analysis, or $Y_i(t) = X_i(t)$ from a different lead providing for inter-lead crossbispectral analysis.

In step 908, the Discrete Fourier transform (DFT) $X_i(f)$ and $Y_i(f)$ of each record of the k selected records, is computed using a standard IEEE library routine or any other publicly available routine in step 908.

In step 910, the power spectra $P_{xi}(f)$ and $P_{yi}(f)$ of each record of the k selected records is computed by

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squaring the magnitudes of each element of the Fourier transform $X_i(f)$ and $Y_i(f)$ respectively.

The system computes the average complex triple product in step 912 by utilizing the following equations where $bc_i(f_1,f_2)$ is an individual complex triple product from one record and $BC(f_1,f_2)$ is the average complex triple product over all records:

$$bc_i(f_1,f_2) = X_i(f_1) * Y_i(f_2) * Y_i^*(f_1+f_2)$$

where $Y_i^*(f_1+f_2)$ is the complex conjugate of $Y_i(f_1+f_2)$.

$$BC(f_1,f_2) = \frac{1}{k} \sum_{i=1}^{k} bc_i(f_1,f_2)$$

The average real triple product is computed in step 914 by using the following equations where $br_i(f_1,f_2)$ is an individual real triple product from one record and $BR(f_1,f_2)$ is the average real triple product over all records:

$$br_i(f_1,f_2) = P_{xi}(f_1) * P_{yi}(f_2) * P_{yi}(f_1+f_2)$$

$$BR(f_1,f_2) = \frac{1}{k} \sum_{i=1}^{k} br_i(f_1,f_2)$$

In step 916, the auto/crossbispectral density array ($BD(f_1,f_2)$) is computed using the following equation:

$$BD(f_1,f_2) = |BC(f_1,f_2)|$$

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In step 918, the system computes the auto/crossbiphase array ($\varphi(f_1,f_2)$) using the following equation:

$$\varphi(f_1,f_2) = \tan^{-1}\left[\mathrm{Im}(BC(f_1,f_2))/\mathrm{Re}(BC(f_1,f_2))\right]$$

$$0 < \varphi < 2\pi \text{ (radians)}$$

In step 920, the system computes the auto/crossbicoherence array ($R(f_1,f_2)$) using the following equation:

$$R(f_1,f_2) = BD(f_1,f_2)/[BR(f_1,f_2)]^{1/2}$$

$$0 < R < 1$$

In step 922, the system returns the requested auto/cross bispectral density, average real triple product, bicoherence, and biphase arrays to the monitor module 402.

Now turning to Fig. 10, a parametric based method for producing the autobispectrum and the crossbispectrum will now be described. In steps 1002, 1004, and 1006 the system sets the symmetries and time series records in the same manner as described above in steps 902, 904, and 906, respectively. The power spectra of $X_i(t)$ and $Y_i(t)$ are estimated in steps 1008, 1010, and 1012. This estimation method includes two major stages, the autoregressive (AR) model order selection and the power spectrum computation for $X_i(t)$ and $Y_i(t)$. In step 1008, the system computes two sequences of autocorrelations, $\{R_{2X}(m)\}$ and $\{R_{2Y}(m)\}$ using the following equation.

$$R_{2z}(m) = \frac{1}{M * N}\sum_{i=1}^{M}\sum_{t=0}^{N-|m|} z_i(t)z_i(t+m), \quad m = 0, 1, \ldots, L, \quad z_i = X_i, Y_i$$

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where M is the number of records (k in our case), and N is the number of samples per record (160 in our case). L is much greater than the possible AR filter order (we choose 50).

The Final Prediction Errors, $FPE_X(m)$ and $FPE_Y(m)$ are calculated for all orders, m = 1, 2, ... L, by performing a Levinson recursion function on each autocorrelation sequence in step 1010 in order to find the order of the AR filter. The locations, Q_X and Q_Y, of the minimum of $FPE_X(m)$ and $FPE_Y(m)$ respectively are chosen to be the orders of the AR filters of power spectra of $X_i(t)$ and $Y_i(t)$ respectively, i.e.,

$$FPE_X(Q_X) = \min \{FPE_X(m)\} \quad \text{and} \quad FPE_Y(Q_Y) = \min \{FPE_Y(m)\}$$

Once the orders of the AR filters for power spectra are chosen, the autocorrelation sequences, $\{R_{2X}(m)\}$ and $\{R_{2Y}(m)\}$, are entered into Levinson recursion with order Q_X and Q_Y, respectively, instead of L. The coefficients, $\{c_{iX}, i=0, 1, \ldots, Q_X\}$ and $\{c_{iY}, i = 0,1, \ldots, Q_Y\}$, obtained from the recursion are the coefficients of the AR filters for power spectra of $X_i(t)$ and $Y_i(t)$ respectively. Then, in step 1012, the power spectrum, $P_z(f)$, is computed as the prediction error (σ_z^2) divided by square of the magnitude of the Fourier transform of the coefficients, i.e.,

$$P_z(f) = \frac{\sigma_z^2}{\left| 1 + \sum_{i=1}^{Q_z} c_{iz}\, e^{-j2\pi fi} \right|^2}, \qquad z = X, Y.$$

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The system estimates the auto/cross bispectrum in steps 1014, 1016, and 1018. The estimation process includes two major stages: the order selection and bispectrum computation. In step 1014, two sequences of third-order moments, $\{R_{3X}(\tau)\}$ and $\{R_{3Y}(\tau)\}$ are computed using the following equation.

$$R_{3z}(\tau) = \frac{1}{y\ *N} \sum_{i=1}^{y} \sum_{t=s_1}^{s_2} z_i(t) z_i^2(t+\tau), \quad z = X, Y, \text{ and } \tau = -L, \ \ldots, \ L$$

where $s_1 = \max(1, 1-\tau)$, $s_2 = \min(N, N-\tau)$, and L is much greater than the possible AR filter orders (e.g. 50).

In step 1016, two super matrices T_X and T_Y are formed as follows.

$$T_z = \begin{pmatrix} R_{3z}(-L) & R_{3z}(-L+1) & \ldots & R_{3z}(0) \\ R_{3z}(-L-1) & R_{3z}(-L) & \ldots & R_{3z}(-1) \\ \cdot & \cdot & \ldots & \cdot \\ R_{3z}(-2L) & R_{3z}(-2L+1) & \ldots & R_{3z}(-L) \end{pmatrix}, \qquad z = X, \ Y.$$

From the assumption we made about the AR filter of bispectrum, the orders O_X and O_Y of the AR filters of bispectra of $X_i(t)$ and $Y_i(t)$ are the ranks of the super matrices T_X and T_Y. Therefore, O_X and O_Y are chosen by using singular value decomposition. Having found the orders, we obtain the coefficients of the AR filters of bispectra by solving the following linear system of equations:

$$\begin{pmatrix} R_{3z}(0) & R_{3z}(1) & \ldots & R_{3z}(O_z) \\ R_{3z}(-1) & R_{3z}(0) & \ldots & R_{3z}(O_z-1) \\ \cdot & \cdot & \ldots & \cdot \\ R_{3z}(-O_z) & R_{3z}(-O_z+1) & \ldots & R_{3z}(0) \end{pmatrix} \begin{pmatrix} 1 \\ b_{1z} \\ \cdot \\ b_{O_z z} \end{pmatrix} = \begin{pmatrix} \beta_z \\ 0 \\ \cdot \\ 0 \end{pmatrix}, \qquad z = X, \ Y.$$

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where the skewness (β_z) and the coefficients (b_{1z}, ..., $b_{o_z z}$), z = X, Y, can be obtained by solving the linear system of equations.

The auto/cross bispectrum of $X_i(t)$ and $Y_i(t)$ are computed in step 1018 as the cubic root of the triple product of the skewnesses $(\beta_X\beta_Y\beta_Y)^{1/3}$ divided by the triple product of the Fourier transforms of the AR filter coefficients ($H_z(f)$), i.e.,

$$BC(f_1, f_2) = (\beta_X\beta_Y\beta_Y)^{1/3} / H_X(f_1)H_Y(f_2)H_Y^*(f_1+f_2)$$

$$H_z(f) = 1 + \sum_{i=1}^{o_z} b_{iz}\, e^{-j2\pi fi}, \qquad z = X, Y.$$

and $BR(f_1, f_2)$ is the real triple product for that same lead:

$$BR(f_1, f_2) = P_X(f_1) * P_Y(f_2) * P_Y(f_1+f_2)$$

After obtaining power spectrum and auto/cross bispectrum, the system computes the bispectral density array, the biphase, and the bicoherence in step 1020 the same way as in steps 916, 918, 920. In step 1022, the system returns to the monitor module 402 the requested bispectral density, biphase, and bicoherence arrays.

For illustration purposes Fig. 11 contains sample autobispectral arrays of the QRS complex showing frequency pairs $0 < f_1 < 512$ Hz, and $0 < f_2 < 256$ Hz. A bispectral density array is shown in Fig. 11(a) where the Z axis represents the magnitude in decibels (db) of the coupling interaction between all appropriate frequency pairs f_1 and f_2. Recall that the frequency pairing scheme must adhere to symmetry rule:

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$$f_1 + f_2 < N/2$$

where N = 1024 Hz in this case. A biphase array is shown in Fig. 11(b) where the Z axis represents the phase in radians of the coupling interaction between all appropriate frequency pairs f_1 and f_2. A bicoherence array is shown in Fig. 11(c) where the Z axis represents the normalized magnitude in percent (%) of the coupling interaction between all appropriate frequency pairs f_1 and f_2.

Referring now to Fig. 12 a more detailed outline of the diagnostic index generation module 410 is shown. In step 1202, the software identifies the type of diagnostic test in progress. The possible options include but are not limited to:

1. detection and quantification of coronary artery disease
2. detection and monitoring of myocardial ischemia
3. detection of reperfusion status post thrombolytic therapy
4. assessment of coronary artery restenosis after successful percutaneous transluminal coronary angioplasty
5. one-time or continuous monitoring of changes in cardiac electrical stability whether due to drugs, heart disease, acute infarction or neural factors.
6. one-time or continuous assessment of antiarrhythmic drug effects on cardiac electrical stability

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7. assessment of the extent of malignancy of cardiac arrhythmias.

8. differentiation of sustained ventricular tachycardia from wide complex supraventricular tachycardia.

9. one time or continuous monitoring of neural inputs to the heart

10. evaluation of pump function and ejection fraction

11. identifying ongoing organ rejection in cardiac transplant patients

In step 1204, the system retrieves the type of bispectral array to use in the diagnostic index computation as well the lead(s) of origin. We have 16 possible ECG leads and each lead could have 4 autobispectral arrays and 4 crossbispectral arrays for any portion of the complexes matching the template selected. These arrays do not include inter-lead crossbispectral arrays. The combination possibilities can lead to a very large number of computations associated with each diagnostic index as well as a substantial reference clinical database. Statistical methods to identify leads and bispectral arrays with the greatest diagnostic fidelity for each test are used to make this system practical. Such statistical methods will be discussed in greater detail below.

In step 1206, the appropriate reference array is retrieved from resident memory or from disk. Each reference array will contain the locations of the frequency pairs which are most sensitive to the diagnostic test in progress. In step 1208, all data points in the bispectral

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array at the locations identified by the retrieved reference array are added together for a single value index. A counter (NP) of the total number of points added is kept. In step 1210, the single value index is divided by NP to obtain the diagnostic index. In step 1212, the program returns to the monitor module 402.

The predetermined clinical reference arrays referred to above are critical to the device's ability to achieve clinically relevant diagnostic efficacy, and the process adopted for generating these clinical reference arrays will now be described. Since the total number of possible diagnostic applications will require many reference arrays, only two types of statistical approaches will be discussed in detail. All other reference arrays are acquired in a similar fashion utilizing a wide number of clinically appropriate statistical approaches. For illustration purposes the generation of the bicoherence reference array for detection of coronary artery disease with orthogonal lead X, assessment of risk to VT/VF with orthogonal lead Z, and assessment of ejection fraction with orthogonal lead X will be discussed in the following section.

In a first study raw ECG signals were acquired from two groups of subjects:

a) young, medically healthy normal volunteers (n=28)

b) older patients with normal conventional ECG's and angiography-proven coronary atherosclerosis (n=16)

The acquisition procedure described previously is followed:

- Band pass filter 0.05-512 Hz
- Sampling rate 1024 sample/sec

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- Number of bispectral averages performed k=100

For all subjects three minutes of artifact free ECG data were acquired. An autobicoherence array is generated from 100 QRS complexes from orthogonal lead X for all subjects. The arrays are grouped in 2 sets of arrays, the first representing the young normals and the second representing the coronary artery disease subjects.

A paired Student's t test is performed on each of 1640 data points, comparing the first and second sets of arrays. The resulting 1640 t values are stored in a two dimensional array identical in structure to that of the bicoherence array.

Each t value from t array (T(f1,f2)) is tested for significance based on the number of degrees of freedom. Where the degrees of freedom are equal to the total number of subjects-1. All t values not meeting the required significance level are set to 0. In the preferred embodiment all locations with a t value not corresponding to a $p < 0.05$ are set to 0.

The application of the above conditions has the effect of identifying all of the frequency pair locations that are significantly different in coronary artery patients when compared to young normal volunteers. Suppression of all other frequency pairs allows easier inspection of the most sensitive regions.

Turning now to Fig. 13, Fig. 13(a) shows the mean autobicoherence array for orthogonal lead X for the normal subjects. Fig. 13(b) shows the mean autobicoherence array for orthogonal lead Y for the CAD subjects. Fig. 13(c) shows the t array with all t values not meeting $p < 0.05$ set to 0.

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The next step involves sorting the t array for the most sensitive ensemble of frequency pair locations. In a preferred embodiment this would consist of the top 25% of all significant t values. The locations f1,f2 of the most significant t values will be used to generate a diagnostic index for each subject in the process described above. Fig. 14(a) shows sample indices for normal subjects and Fig. 14(b) shows sample indices for CAD subjects. The coded filename of the subject tested precedes each index.

The final step is to identify a cutoff value for the diagnostic index above which subjects are normal and all values below will indicate the presence of CAD. This cutoff should be optimized to yield the best sensitivity and specificity.

$$Sensitivity = \frac{true\ positive\ tests}{all\ true\ positives}$$

$$Specificity = \frac{true\ negative\ tests}{all\ true\ negatives}$$

In this particular case if we chose a cutoff of 20.0 the sensitivity and specificity will be 100%(16/16) and 96.4%(27/28) respectively.

The above statistical steps are repeated for all the possible bispectral arrays that can be generated (as described above) from all ECG leads acquired. To rank order the arrays with respect to diagnostic efficacy a second prospective study is conducted. The conditions under which the study is conducted are identical to those of the first except that: a) the frequency pair locations of interest have already been identified and are now

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followed prospectively and b) the size of the study group is now sufficiently large so that sample variation of bispectral arrays more closely approximates the true variance within the population undergoing the intervention or suffering from the disease.

Thus for the example of coronary artery diagnosis, patients undergoing coronary angiography would each have a recording taken. The diagnostic index for each type of bispectral array from each lead or combination of leads would be calculated. These indices would then be compared to the results of angiography. The sensitivities and specificities for the detection of coronary disease would then be calculated for each bispectral array. The best array and lead system is then chosen as the default setting for the diagnostic procedure under consideration. The frequency locations identified by t values of this array will be used by the diagnostic index derivation module 410.

The above statistical approach may also be used to identify patients who are at risk of malignant arrhythmias. In a second study two new groups of patients are used:

a) The control group consists of patients with previous anterior or inferior MI without a history of malignant ventricular arrhythmias (n=37).

b) The arrhythmia group consists of patients with a history of previous anterior or inferior MI and a history of sustained ventricular tachycardia or out-of-hospital cardiac arrest (VT/VF) (n=12).

An autobicoherence array is generated from 100 QRS complexes from orthogonal lead Z for all subjects. The

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arrays are grouped in 2 sets of arrays, the first representing the MI subjects and the second representing the VT/VF subjects. After conducting the t test described earlier the statistical data shown in Fig. 15 was generated. Fig. 15(a) shows the mean autobicoherence array for orthogonal lead Z for the MI subjects. Fig. 15(b) shows the mean autobicoherence array for orthogonal lead Z for the VT/VF subjects. Fig. 15(c) shows the t array with all t values not meeting $p < 0.05$ set to 0.

The t array generated is then used to produce diagnostic indices for both groups as shown earlier for the CAD study. The whole statistical process is followed through including prospective studies to identify the best bispectral array and its corresponding lead for the identification of patients who are at risk of malignant arrhythmias. Fig. 16(a) shows sample indices for MI subjects and Fig. 16(b) shows sample indices for the VT/VF subjects. The coded filename of the subject tested precedes each index. In this particular case if we chose a cutoff of 26.0, the sensitivity and specificity will be 91.6%(11/12) and 86.4%(32/37) respectively.

This invention is not limited to the use of the t test and many other statistical ranking tests might be used when appropriate. For example if the diagnostic procedure requires the measurement of a continuous variable such as ejection fraction (EF) regression analysis is more suitably used.

The following example will describe the use of the present invention to measure a continuous variable. In this example, raw ECG signals were acquired from a large number of patients (n=247) with known EF through ventriculography. The autobicoherence array from 100 QRS

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complexes for lead X was computed. Each one of the 1640 bicoherence points was correlated with its corresponding EF value across all patients. The outcome is a two dimensional array similar in structure to that of the bicoherence array and where the value at each (f1,f2) represents the r regression coefficient between the bicoherence at this frequency pair and ejection fraction. The r coefficient will range from -1 to 1. The results are shown in Fig. 17. Fig. 17(a) shows the positive r values between EF and bicoherence at the corresponding frequency pairs, and Fig. 17(b) shows the negative r values.

In addition to quantifying the presence and extent of coronary artery disease (CAD), myocardial ischemia, cardiac electrical stability, risk of malignant ventricular arrhythmia, site(s) of origin of malignant arrhythmias, extent of malignancy of arrhythmias, degree of antiarrhythmic drug efficacy, neural and humoral inputs to the heart, pump function/ ejection fraction, and ongoing organ rejection in cardiac transplant patients, the system and method of the present invention may also be used to assess a myriad of cardiac phenomena based on the acquisition and processing of ECG signals into various bispectral arrays which are then compared to appropriate reference arrays.

Although power spectral analytic techniques in the frequency domain have been applied to the ECG signal, as was discussed in the Background above, higher order spectra whether by FFT or by parametric approaches have never been so applied. No bispectral technique has ever been demonstrated to be useful for any diagnostic purpose. Other techniques for the quantification of coronary artery disease, PTCA restenosis or the detection of cardiac electrical instability, especially as it changes with

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antiarrhythmic drug administration, remain qualitative, static and limited in their overall utility and acceptance in practice. Specifically, the system and method of the present invention uses various bispectral values to measure dynamic frequency structure [higher order phase-locking] across all frequency pairs in a frequency range ignored by those knowledgeable in the art and uses various alterations in these bispectral parameters at a limited number of frequency locations as an index of physiological perturbation. The system and method utilizes various bispectral arrays of transformed ECG signals of defined clinical populations to define the locations of the subset of frequencies used to calculate this index. Reference clinical arrays are further utilized to assess the meaning of this index and to measure the significance of deviations of this index from normality. This allows the quantitative gauging of the disturbances in cardiac function, whether due to coronary disease, electrical instability, restenosis after PTCA, drugs or ischemia for any particular ECG lead position. The invention disclosed here also defines the graphic display of the diagnostic index, whether on video screen or on paper, whether in real-time or in digital archive.

While the foregoing invention has been described with reference to its preferred embodiments, various alterations and modifications will occur to those skilled in the art. For example, the ECG may carry diagnostic information at frequencies much higher then the cutoff frequency of 512 Hz. The use of such high frequency low energy components of the ECG waveform by the system and method described above is intended to fall within the scope of the current invention. All such alterations and modifications are intended to fall within the scope of the appended claims.

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What is claimed is:

1. A method of noninvasively detecting cardiac phenomena comprising the steps of:

acquiring electrocardiographic signals from a body surface of a subject being analyzed through a surface electrode;

determining a waveform template representing a QRST waveform in said subject;

selecting a number of signals that match said waveform template and storing said signals for processing;

generating bispectral values from selected signals that can be used to analyze cardiac phenomena.

2. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said generated bispectral values are autobispectral density values.

3. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said generated bispectral values are autobicoherence values.

4. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said generated bispectral values are autobiphase values.

5. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said step of selecting a number of signals that match said waveform template comprises the step of selecting pairs of successive time series records that are used in the generation of bispectral values.

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6. The method of noninvasively detecting cardiac phenomena of claim 5 wherein said generated bispectral values are crossbispectral density values.

7. The method of noninvasively detecting cardiac phenomena of claims 5 wherein said generated bispectral values are crossbicoherence values.

8. The method of noninvasively detecting cardiac phenomena of claim 5 wherein said generated bispectral values are crossbiphase values.

9. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to detect a presence and extent of coronary artery disease in said subject.

10. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to detect a presence and extent of myocardial ischemia in said subject.

11. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to analyze cardiac electrical stability in said subject.

12. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to analyze a risk of malignant ventricular arrhythmia in said subject.

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13. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to locate a site of origin of malignant arrhythmias in said subject.

14. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to analyze an extent of malignancy of arrhythmias in said subject.

15. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to evaluate a degree of antiarrhythmic drug efficacy in said subject.

16. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to examine neural and humoral inputs to the heart of said subject.

17. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to evaluate pump function or ejection fraction in the heart of said subject.

18. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of using said bispectral values to monitor ongoing organ rejection wherein said subject is a cardiac transplant patient.

19. The method of noninvasively identifying and distinguishing wide-complex supraventricular tachycardia from sustained ventricular tachycardia.

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20. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said step of generating bispectral values comprises:

assigning each selected signal matching said waveform template to a time series record;

computing an average complex triple product using Fourier transforms of said time series records;

computing biphase values as the inverse tangent of the quotient of an imaginary part of the average complex triple product divided by a real part of the average complex triple product.

21. The method of noninvasively detecting cardiac phenomena of claim 20 wherein said biphase values are crossbiphase values.

22. The method of noninvasively detecting cardiac phenomena of claim 20 wherein said biphase values are autobiphase values.

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23. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said step of generating bispectral values comprises:

assigning each selected signal matching said waveform template to a time series record;

determining Fourier transforms of said time series records;

estimating bispectrum of said time records by computing sequences of third-order moments, forming super matrices using said third-order moments, determining orders of autoregressive model filters of the bispectrum of the Fourier transforms of said time records from ranks of said super matrices, obtaining the skewness and autoregressive filter coefficients by solving a set of equations based on said third order moments and said orders, and computing said bispectrum from said skewness and autoregressive filter coefficients.

24. The method of noninvasively detecting cardiac phenomena of claim 23 further comprising the step of estimating power spectra of said Fourier transforms, said step of estimating power spectra comprising the steps of:

computing two sequences of autocorrelations and performing a recursion function on each autocorrelation sequence in order to determine final prediction errors, minimums of said final prediction errors being orders of the autoregression filters of said power spectra;

performing a recursion function on said autocorrelation sequences using said orders of the autoregression filters in order to generate coefficients of said autoregression filters;

computing the power spectra as the final prediction error divided by a square of the magnitude of the Fourier transform of said coefficients.

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25. The method of noninvasively detecting cardiac phenomena of claim 23 wherein said step of computing bispectrum of said Fourier transforms of said time series records comprises dividing the cubic root of the product of three skewnesses by a triple product of the Fourier transforms of the AR filter coefficients.

26. The method of noninvasively detecting cardiac phenomena of claim 23 further comprising the step of computing an array of bispectral densities by determining the absolute value for each bispectrum value.

27. The method of noninvasively detecting cardiac phenomena of claim 23 further comprising the step of computing an array of biphase values as the inverse tangent of the quotient of an imaginary part of the bispectrum divided by a real part of the bispectrum.

28. The method of noninvasively detecting cardiac phenomena of claim 24 further comprising the steps of:

computing a real triple product as the product of three power spectra values;

computing an array of bicoherence values as the quotient of bispectral density divided by a square root of said real triple product.

29. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said bispectral values are crossbispectral values generated from consecutive signals from one surface electrode.

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30. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said bispectral values are crossbispectral values generated from signals obtained from two surface electrodes.

31. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said template is a sinus rhythm template.

32. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said template is an ectopic beat template.

33. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the steps of generating clinical reference arrays for use in identifying particular bispectral values that are sensitive to the cardiac phenomena being analyzed.

34. The method of noninvasively detecting cardiac phenomena of claim 33 further comprising the step of rank ordering said clinical reference arrays with respect to the diagnostic efficacy of the arrays for the cardiac phenomena being analyzed.

35. The method of noninvasively detecting cardiac phenomena of claim 33 wherein values in said clinical reference arrays that are not significant are suppressed to facilitate inspection of the most sensitive values.

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36. The method of noninvasively detecting cardiac phenomena of claim 33 further comprising the steps of determining a diagnostic index from said clinical reference array, generated values above said index indicating a normal condition and below said index indicating an abnormal condition.

37. The method of noninvasively detecting cardiac phenomena of claim 36 wherein said diagnostic index is optimized to yield the best sensitivity and specificity with sensitivity being equal to true positives divided by positives and specificity being equal to true negatives divided by negatives.

38. A system for noninvasively detecting cardiac phenomena comprising:

means for acquiring electrocardiographics signals from a surface of a body of a subject being analyzed;

means for determining a waveform template representing a normal QRST waveform in said subject;

means for selecting a number of signals that match said waveform template;

means for storing said signal portions for processing;

means for generating bispectral values from selected signals that can be used to analyze cardiac phenomena.

39. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said bispectral values are crossbiphase values.

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40. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said bispectral values are autobiphase value.

41. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are autobispectral density values.

42. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are crossbispectral density values.

43. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are autobicoherence values.

44. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are crossbicoherence values.

45. The system for noninvasively detecting cardiac phenomena of claim 1 wherein said means for acquiring electrocardiographic signals is a plurality of surface electrodes and wherein said bispectral values are crossbispectral values generated from consecutive signals from one surface electrode.

46. The system for noninvasively detecting cardiac phenomena of claim 38, wherein said means for acquiring electrocardiographic signals is a plurality of surface electrodes and wherein said bispectral values are crossbispectral values generated from signals obtained from two of said surface electrodes.

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47. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said template is an ectopic beat template.

48. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for generating clinical reference arrays for use in identifying particular bispectral values that are sensitive to the cardiac phenomena being analyzed.

49. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for automatically rank ordering said clinical reference arrays with respect to diagnostic efficacy of the arrays for the cardiac phenomena being analyzed.

50. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for suppressing values in said clinical reference arrays that are not significant in order to facilitate inspection of the most sensitive values.

51. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for determining a diagnostic index from said clinical reference arrays, generated values above said index indicating a normal condition and values below said index indicating an abnormal condition.

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52. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said diagnostic index is optimized to yield the best sensitivity and specificity with sensitivity being equal to true positive tests divided by all true positives and specificity being equal to true negative tests divided by all true negatives.

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AMENDED CLAIMS
[received by the International Bureau
on 21 December 1990 (21.12.90);
original claims 1,9-19,38,40,45,48-52 amended;
new claims 53-56 added; other claims unchanged (8 pages)]

1. A method of noninvasively detecting cardiac phenomena comprising the steps of:

acquiring electrocardiographic signals from a body surface of a subject being analyzed through a surface electrode;

determining a waveform template representing a QRST waveform in said subject;

selecting a number of signals that match said waveform template and storing said signals for processing;

generating bispectral values from selected signals, and comparing said bispectral values to reference bispectral values to analyze cardiac phenomena.

2. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said generated bispectral values are autobispectral density values.

3. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said generated bispectral values are autobicoherence values.

4. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said generated bispectral values are autobiphase values.

5. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said step of selecting a number of signals that match said waveform template comprises the step of selecting pairs of successive time series records that are used in the generation of bispectral values.

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6. The method of noninvasively detecting cardiac phenomena of claim 5 wherein said generated bispectral values are crossbispectral density values.

7. The method of noninvasively detecting cardiac phenomena of claims 5 wherein said generated bispectral values are crossbicoherence values.

8. The method of noninvasively detecting cardiac phenomena of claim 5 wherein said generated bispectral values are crossbiphase values.

9. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to detect a presence and extent of coronary artery disease in said subject.

10. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to detect a presence and extent of myocardial ischemia in said subject.

11. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to analyze cardiac electrical stability in said subject.

12. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to analyze a risk of malignant ventricular arrhythmia in said subject.

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13. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to locate a site of origin of malignant arrhythmias in said subject.

14. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to analyze an extent of malignancy of arrhythmias in said subject.

15. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to evaluate a degree of antiarrhythmic drug efficacy in said subject.

16. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to examine neural and humoral inputs to the heart of said subject.

17. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to evaluate pump function or ejection fraction in the heart of said subject.

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18. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of comparing said bispectral values to reference bispectral values to monitor ongoing organ rejection wherein said subject is a cardiac transplant patient.

19. The method of noninvasively detecting cardiac phenomena of claim 1 further comprising the step of identifying and distinguishing wide-complex supraventricular tachycardia from sustained ventricular tachycardia.

20. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said step of generating bispectral values comprises:

assigning each selected signal matching said waveform template to a time series record;

computing an average complex triple product using Fourier transforms of said time series records;

computing biphase values as the inverse tangent of the quotient of an imaginary part of the average complex triple product divided by a real part of the average complex triple product.

21. The method of noninvasively detecting cardiac phenomena of claim 20 wherein said biphase values are crossbiphase values.

22. The method of noninvasively detecting cardiac phenomena of claim 20 wherein said biphase values are autobiphase values.

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36. The method of noninvasively detecting cardiac phenomena of claim 33 further comprising the steps of determining a diagnostic index from said clinical reference array, generated values above said index indicating a normal condition and below said index indicating an abnormal condition.

37. The method of noninvasively detecting cardiac phenomena of claim 36 wherein said diagnostic index is optimized to yield the best sensitivity and specificity with sensitivity being equal to true positives divided by positives and specificity being equal to true negatives divided by negatives.

38. A system for noninvasively detecting cardiac phenomena comprising:

means for acquiring electrocardiographic signals from a surface of a body of a subject being analyzed;

means for determining a waveform template representing a normal QRST waveform in said subject;

means for selecting a number of signals that match said waveform template;

means for storing said selected signals for processing;

means for generating bispectral values from said selected signals and for comparing said bispectral values to reference bispectral values to detect and analyze cardiac phenomena.

39. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said bispectral values are crossbiphase values.

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40. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said bispectral values are autobiphase values.

41. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are autobispectral density values.

42. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are crossbispectral density values.

43. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are autobicoherence values.

44. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said generated bispectral values are crossbicoherence values.

45. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said means for acquiring electrocardiographic signals is a plurality of surface electrodes and wherein said bispectral values are crossbispectral values generated from consecutive signals from at least one of said plurality of said surface electrodes.

46. The system for noninvasively detecting cardiac phenomena of claim 38, wherein said means for acquiring electrocardiographic signals is a plurality of surface electrodes and wherein said bispectral values are crossbispectral values generated from signals obtained from two of said surface electrodes.

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47. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said template is an ectopic beat template.

48. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for generating clinical reference arrays for use in identifying particular bispectral values that are sensitive to the cardiac phenomena being detected and analyzed.

49. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for automatically rank ordering clinical reference arrays of said reference bispectral values with respect to diagnostic efficacy of the arrays for the cardiac phenomena being detected and analyzed.

50. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for suppressing values in clinical reference arrays of said reference bispectral values that are not significant in order to facilitate inspection of values most likely to indicate the presence of the cardiac phenomena.

51. The system for noninvasively detecting cardiac phenomena of claim 38 further comprising means for determining a diagnostic index from clinical reference arrays of said reference bispectral values, generated values above said index indicating a normal condition and values below said index indicating an abnormal condition.

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52. The system for noninvasively detecting cardiac phenomena of claim 51 wherein said diagnostic index is optimized to yield the best sensitivity and specificity with sensitivity being equal to true positive tests divided by all true positives and specificity being equal to true negative tests divided by all true negatives.

53. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said bispectral values are generated by computing the Fourier transform of the third order autocorrelation function of said filtered signals.

54. The method of noninvasively detecting cardiac phenomena of claim 1 wherein said bispectral values are generated by computing the Fourier transform of the third order crosscorrelation function of said filtered signals.

55. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said means for generating bispectral values comprises a means for computing the Fourier transform of the third order autocorrelation function of said filtered signals.

56. The system for noninvasively detecting cardiac phenomena of claim 38 wherein said means for generating bispectral values comprises a means for computing the Fourier transform of the third order crosscorrelation function of said filtered signals.

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STATEMENT UNDER ARTICLE 19

Claims 1, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 38, 40, 45, 48, 49, 50, 51, and 52 of the above-referenced application have been amended to more clearly describe the subject of the invention and to make them consistent with the amended claims in the priority United States application (which claims have been amended to cure indefiniteness problems), and to correct obvious errors.

Claims 53, 54, 55, and 56 have been added to clearly protect various means for generating bispectral values in applicant's system.

Replacement sheets (pages 39-42 and 46-49) are enclosed for pages containing amended or new claims.

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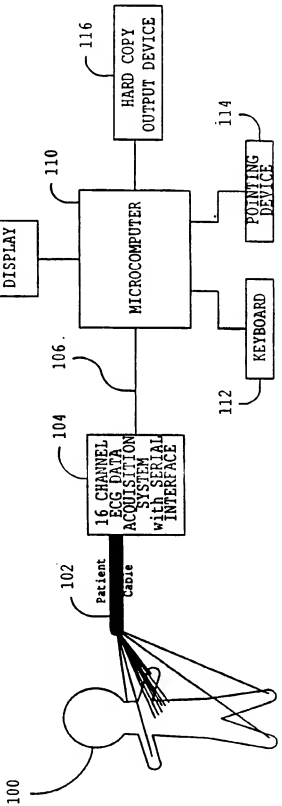
Fig. 1



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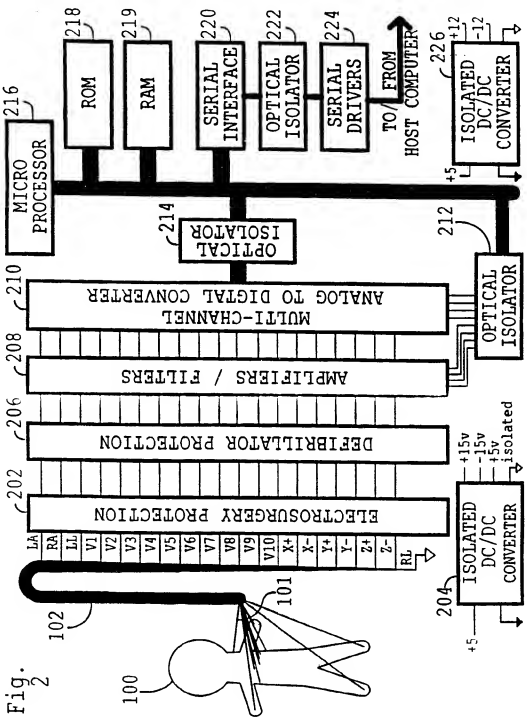

Fig. 2

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Fig. 3

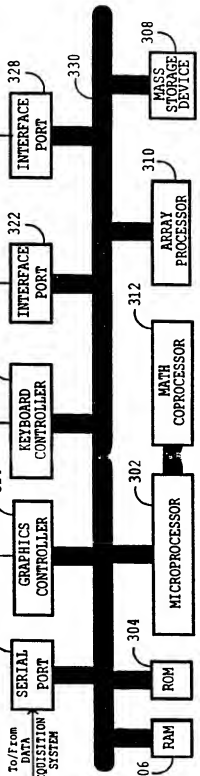

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Fig. 4

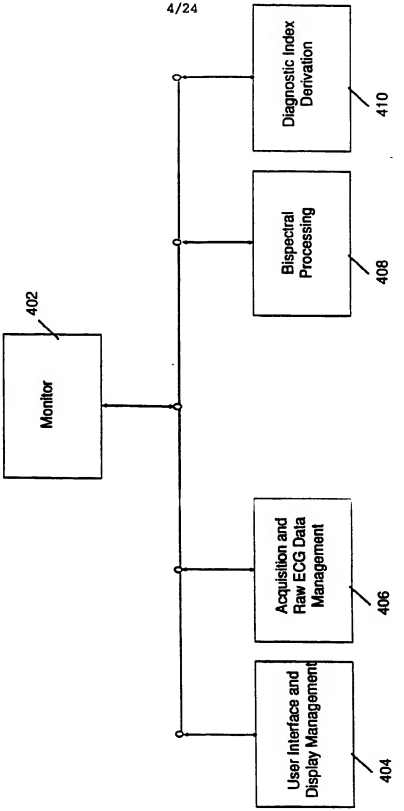

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Fig. 5

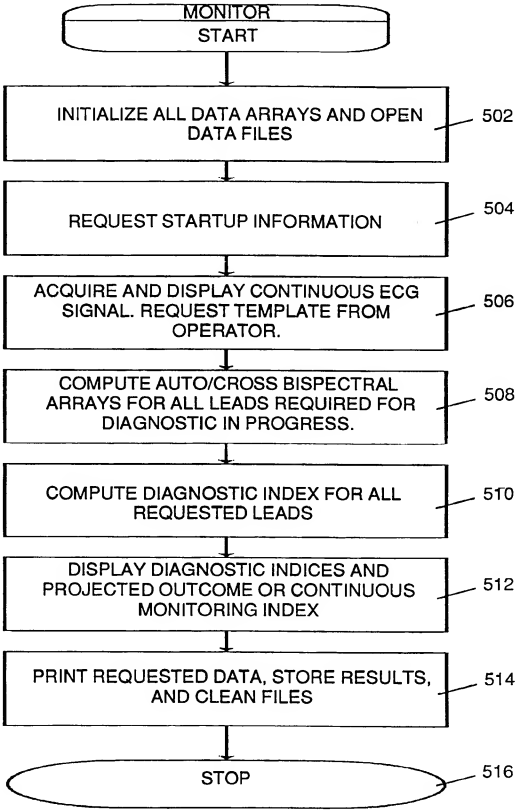

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Fig. 6

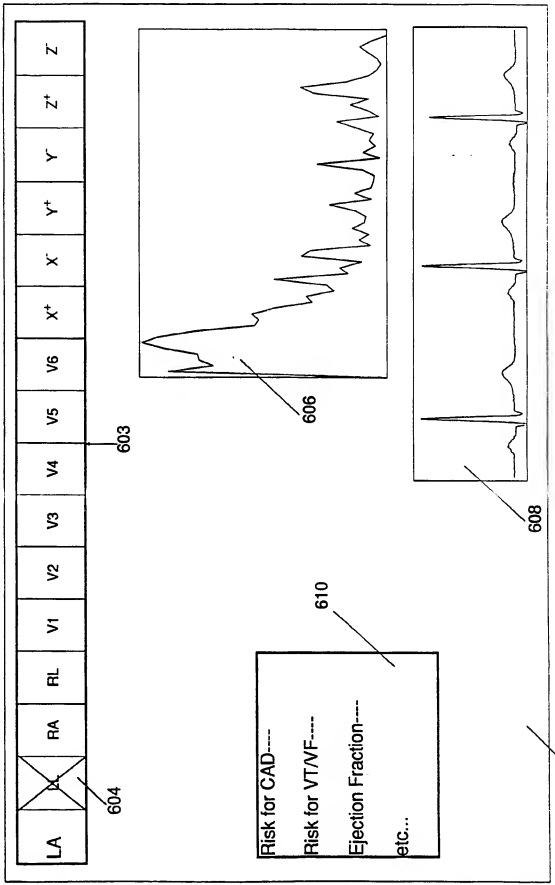

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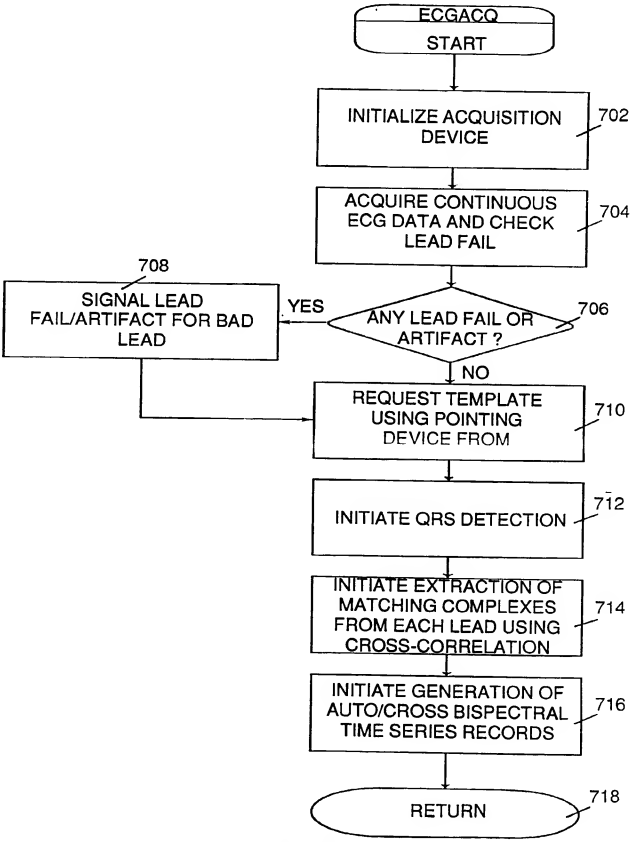
Fig. 7



SUBSTITUTE SHEET

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Fig. 8

Fig. 8(a)

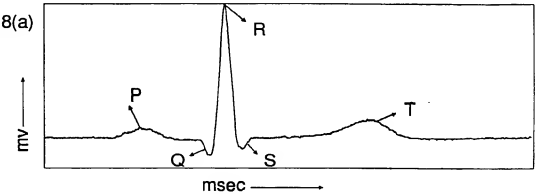

Fig. 8(b)

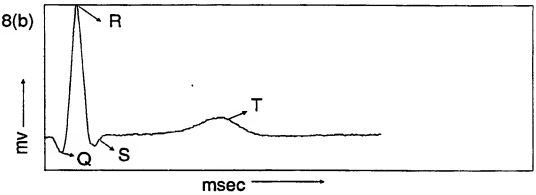

Fig. 8(c)

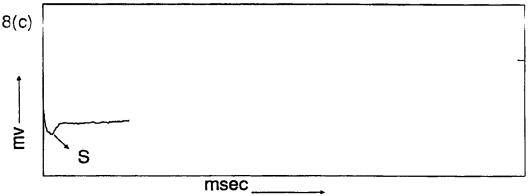

Fig. 8(d)

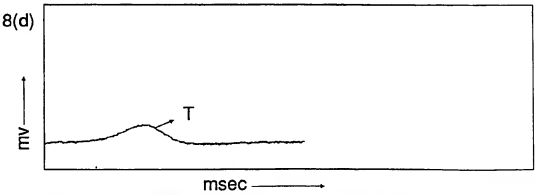

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Fig. 9

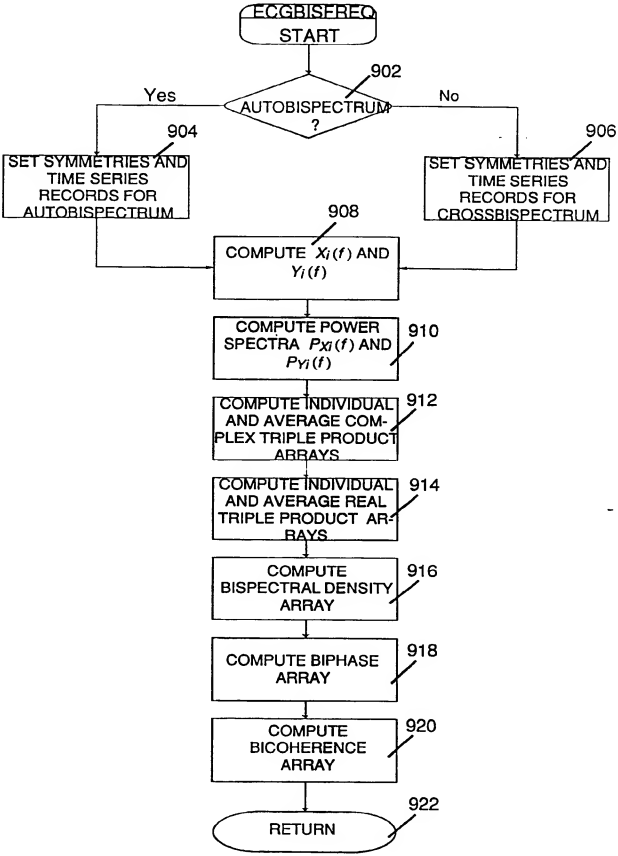

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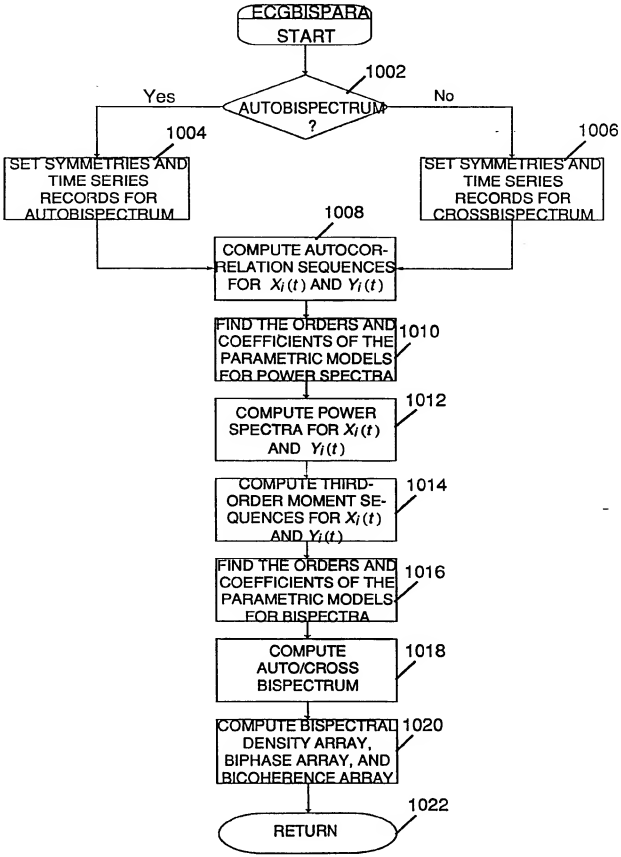
Fig. 10



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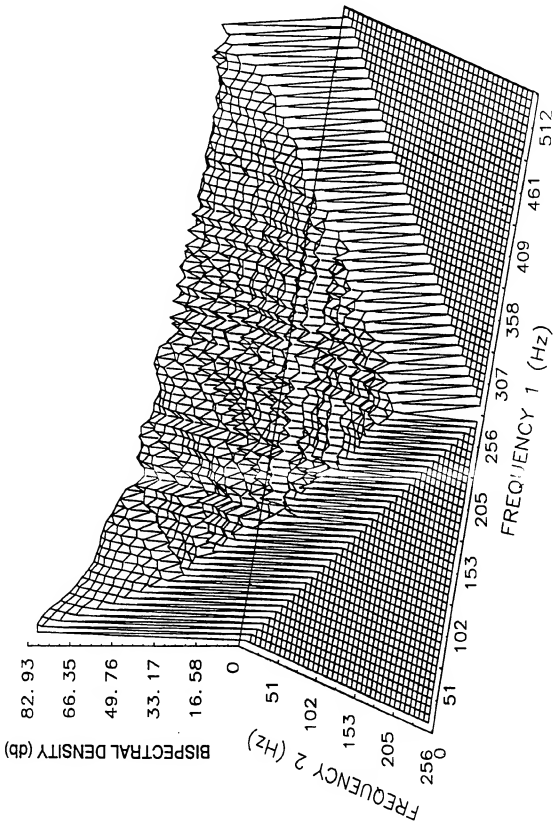

Fig. 11(a)

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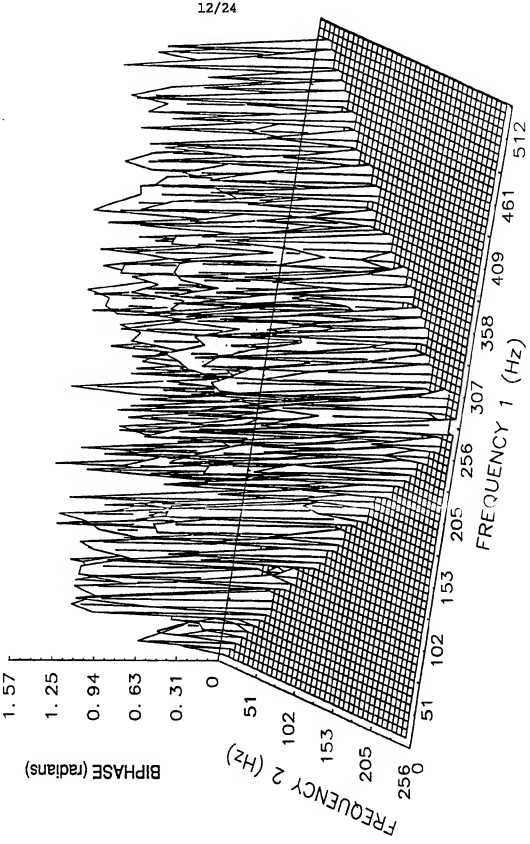

Fig. 11(b)

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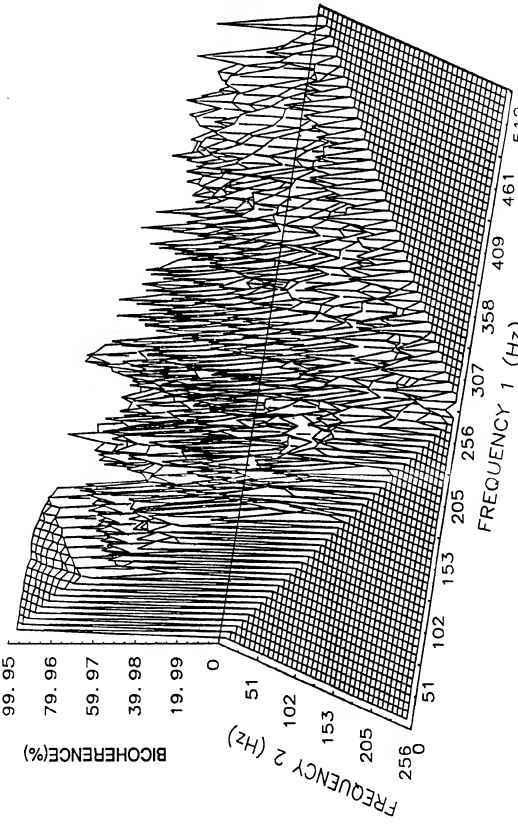

Fig. 11(c)

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Fig. 12

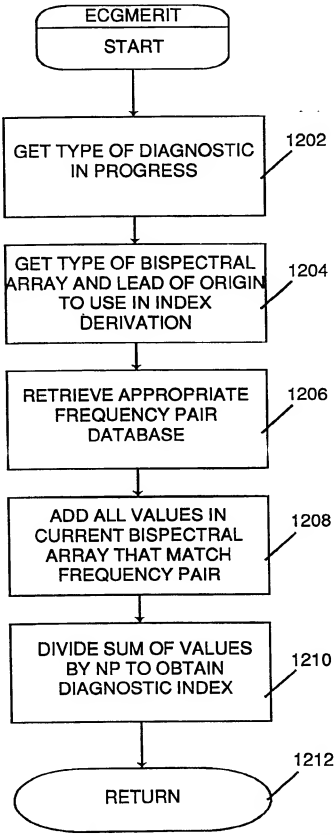

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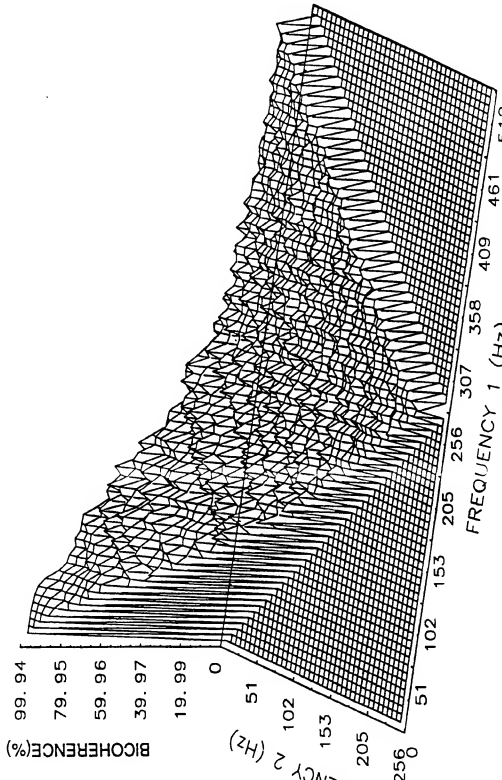
Fig. 13(a)



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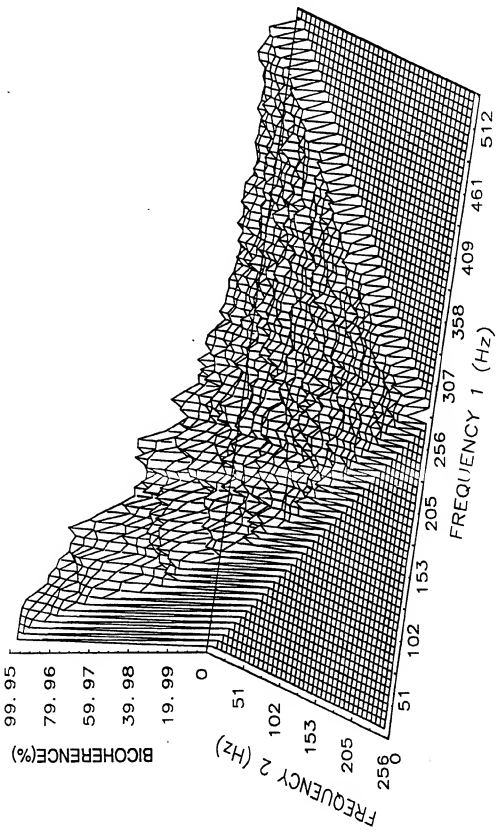

Fig. 13(b)

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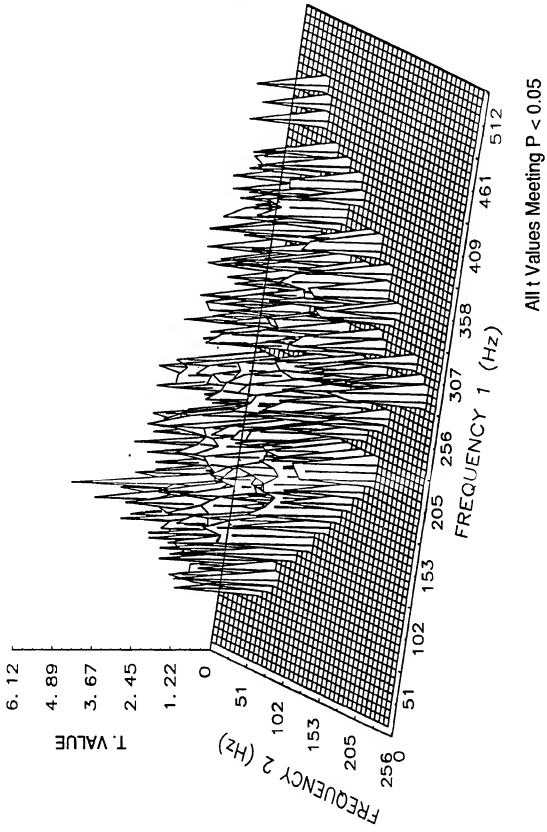

Fig. 13(c)

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Fig. 14(a). Indices for Normal Subjects:

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KIJHJ06A.BY	25.05850220	WEARH09A.BY	25.50495530
BREAA25A.BY	25.78440280	ROMAI20A.BY	26.68617630
LEGNJ07A.BY	27.35936550	AYDKJ17A.BY	28.80974580
KRRXA12A.BY	29.20651050	ALDAI15A.BY	31.61214070
GAKCI08A.BY	33.26648710	ALDSB23A.BY	34.04255680
CAJXH09A.BY	34.30604170	DERXJ11A.BY	34.43464660
SIJEJ07A.BY	36.91619870	LASPI20A.BY	38.84684750
PRDMI08A.BY	41.32183460	KIWWJ06A.BY	42.58206940
SIDSJ06A.BY	46.49957660	LUWJJ11A.BY	47.29038240
KRJLI27A.BY	47.33069610	DODXH25A.BY	53.40213010
LACJB23A.BY	57.13722610	LEKXI20A.BY	62.86845780
PLIMI08A.BY	63.58295440	DAMBE25A.BY	66.79967500

Fig. 14(b). Indices for CAD Subjects:

KERXD04A.by	8.58777046	KWWJB23A.BY	8.90316200
BREJB15A.BY	8.91221237	MARTK28A.BY	10.16669940
LEJJH09A.BY	10.40363500	TEMXA17A.BY	10.51200770
FERSC28B.BY	10.70160010	BEBLI13A.BY	10.83960440
NOJEJ06A.BY	11.20124050	SADJI12A.BY	12.18137650
TRPAD03A.BY	12.62624550	ROGAD18A.BY	12.93428040
COJXD14A.BY	17.09865380	ALNXA24A.BY	18.85142710
MEVRE03A.BY	18.90387920	RINWB14A.BY	18.96992110

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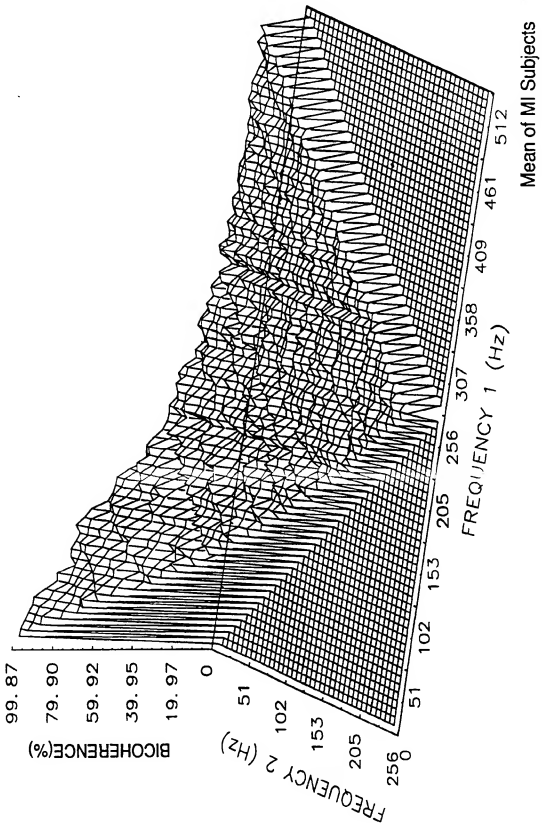

Fig. 15(a)

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Fig. 15(b)

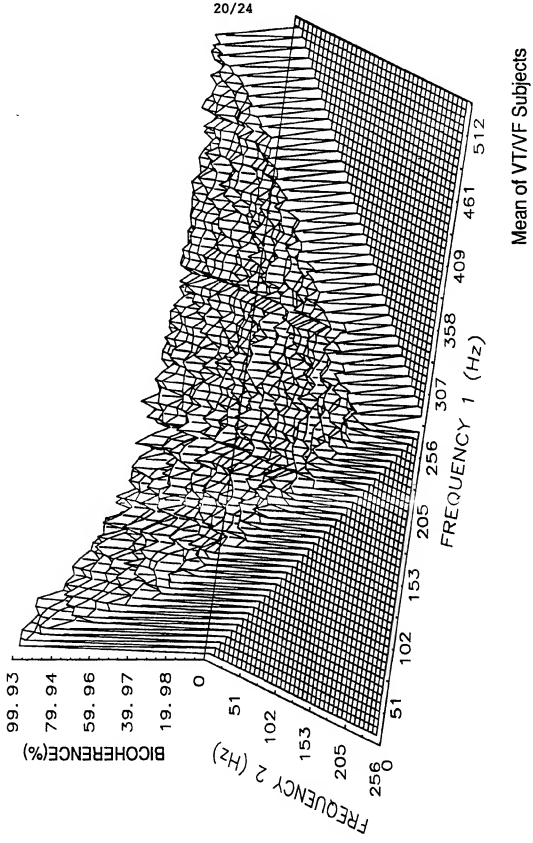

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Fig. 15(c)

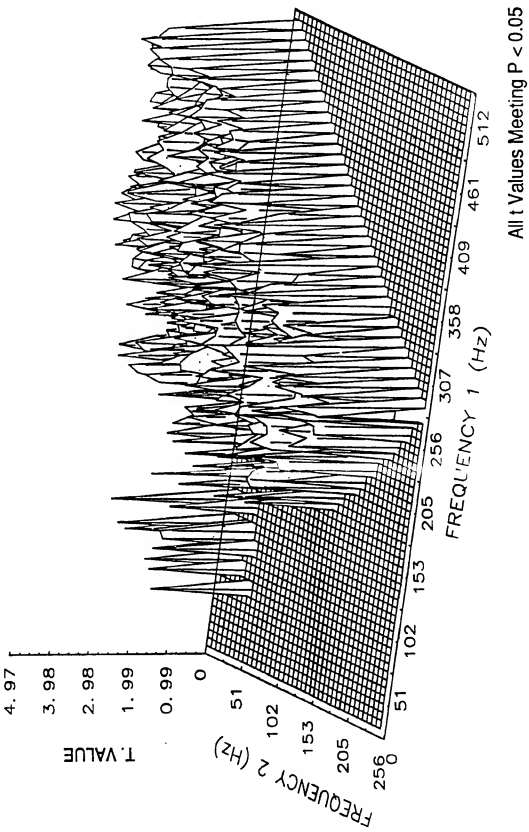

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Fig. 16(a). Indices for MI Subjects:

CAADD19A.BZ	9.00820732	SIVJA12A.BZ	9.01792526
MURJB01A.BZ	9.25046730	MEGBA03A.BZ	9.52403450
DOPTK09A.BZ	9.76105309	VIDAI13A.BZ	9.92419147
BEMGH19A.BZ	11.27546310	MCMCA06A.BZ	11.95668320
KIWFC29A.BZ	12.02414040	BEWJC06A.BZ	12.22941110
PEWJH03A.BZ	12.96870710	STJHJ04A.BZ	13.52073860
MOAHD05A.BZ	14.15726660	GPLEE18A.BZ	14.76358320
BLDHC13A.BZ	14.86789700	DEFGH18A.BZ	15.59866910
DULJB14A.BZ	18.31387140	THMLJ12A.BZ	19.27793310
BACLC29A.BZ	19.73213200	HABBD17A.BZ	19.99048230
MAEJD05A.BZ	21.32853510	PEFLC22A.BZ	21.37274740
SIFJA13A.BZ	21.51948740	BEJAB16A.BZ	21.52597430
SPCHK30A.BZ	22.34267430	BANSH23A.BZ	22.57764820
DAAXK29A.BZ	22.79805180	FRSDC22A.BZ	22.90790940
HAFLB08A.BZ	24.19918440	LEWXI15A.BZ	25.14107320
ALRWA12A.BZ	25.26878550	ALPRK22A.BZ	25.82863240
NOMPA18A.BZ	34.38295360	BERHD05A.BZ	34.66892620
BERJB21A.BZ	40.08743670	TRJFI13A.BZ	46.21981050
HOREB23A.BZ	52.51377110		

Fig. 16(b). Indices for VT/VF Subjects:

DOMIB23A.BZ	20.90007590	LARCD05A.BZ	29.86979290
HEGDI15A.BZ	31.09114650	VASCD10A.BZ	33.72085570
GABMJ03A.BZ	34.00053020	TRVSA31A.BZ	34.75869370
MAEDL14A.BZ	37.54197690	DAHEB15A.BZ	43.78262330
GIRLL21A.BZ	47.85096740	HAWJE22A.BZ	48.92345810
BOJXC21A.BZ	49.29041290	PANHD12A.BZ	61.22085570

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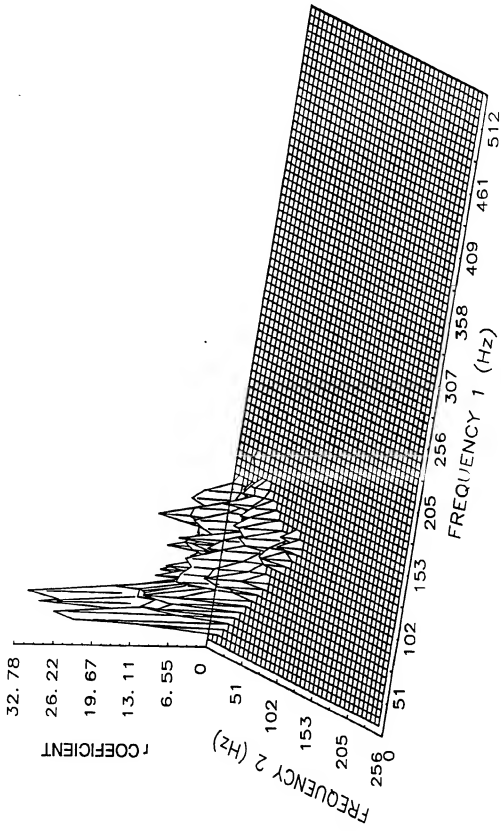
Fig. 17(a)



All Frequency Pairs that Have a Positive Correlation With EF

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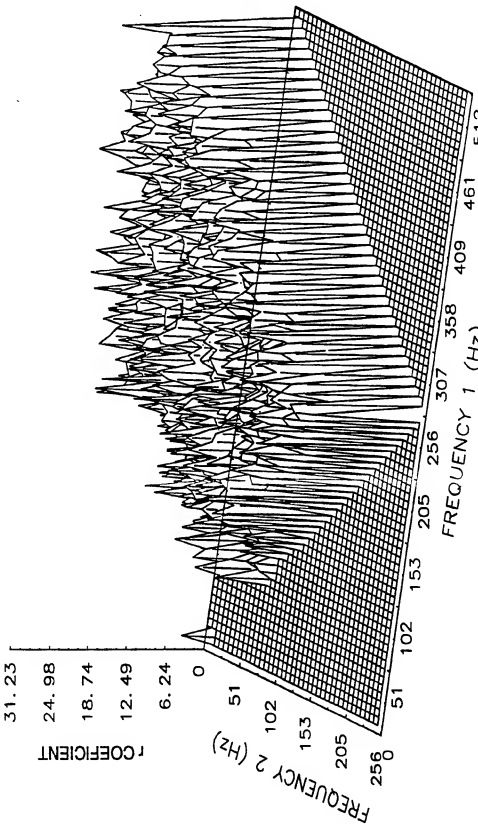

Fig. 17(b)

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/01385

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL. (5) A61B 5/04 U.S. CL. 128/696

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
U.S.	class 128, subclasses 696,697,702,703,708 class 364, subclasses 413.05, 413.06

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,680,708, 14 July 1987 AMBOS et al, See entire document.	1-52
Y	US, A, 4,732,158, 22 March 1988, SADEH, See entire document	1,31,32, 38,47
Y	US, A, 4,742,458, 03 May 1988, NATHANS et al., See entire document.	1-52
Y	US, A, 3,995,622, 07 December 1976, NORDGREN et al., See entire document.	19

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 APRIL 1990	14 JUN 1990
International Searching Authority	Signature of Authorized Officer
ISA/US	G. MANUEL

Form PCT/ISA/210 (second sheet) (Rev.11-87)

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COMPUTER ARRHYTHMIA ANALYSIS IN AN EXERCISE SYSTEM

11.2

P.D. 30-5-1985

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A61B5/0452B

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The University of Michigan Ann Arbor, MI 48109
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SUMMARY

A computer-based system for interpretation of the electrocardiogram for the diagnosis of cardiac rhythm and ST segment abnormality in an exercise system has been developed. Digitized data are analyzed in a beat-by-beat mode and a contextual diagnosis of underlying rhythm is provided. Each beat is assigned a beat code based on waveform analysis and RR interval measurement. Selective signal averaging based on individual beat codes is done for an improved signal-to-noise ratio for accurate ST segment measurement. Template generation, QRS window size, baseline correction, and continuous updating of heart rate have all been automated. ST level and slope measurements were computed on the signal-averaged data. Arrhythmia analysis of 13 passages of abnormal rhythm by computer was found to be correct in 98.4% of all beats. Twenty-one passages of exercise data, one to five minutes in length, were evaluated by the cardiologist and found to be in agreement in 46 of 48 measurements of ST level and 44 of 48 measurements of ST slope.

METHODS AND MATERIALS

Three channels of electrocardiographic (ECG) data (AVF, V5, and V5) from 15 subjects were tape-recorded at the Heart Station of the University of Michigan Hospital at a speed of 3 3/4 ips with Hewlett Packard 3964A FM instrumentation recorder. Patients were connected to a 12-lead electrocardiograph (Cambridge, model CM2000) set to a gain of 1. The ECG signal was subsequently played back for real time processing in the Medical Computing Lab at the University of Michigan. The computer system used for processing is an Intel 8086/8087 processor within an APEX medical computer system (Elscint, Ltd. Model 2000). The configuration consists of the following components: 1 megabyte of on-board memory, multi-channel analog-to-digital(A/D) converter, a 30 megabyte hard disk, and two CRT screens. This nuclear medicine system was specifically configured to incorporate data acquisition of the ECG signal. Data were digitized with 8 bit resolution at a sampling rate of 250 Hz with a maximum input range of ± 5 volts, and were triggered internally for recognition of the QRS waveform. During digitization, strip chart recordings were made of the tape recorded data at a paper speed of 50 mm/sec (Gould 8 channel, Model Brush 481). After processing, the digitized samples were displayed on the strip chart recorder via a digital-to-analog(D/A) subsystem (Thermar Lab Master) with 12-bit resolution. Fourteen pre-recorded passages containing abnormal rhythm were processed to test the arrhythmia analysis portion. Twenty-one passages of one to five minutes in length from recordings of fifteen subjects during exercise stress tests were processed for testing of the overall system. Computer results were given to a cardiologist for validation.

The first stage of the project was the algorithm development for individual beat classification and contextual arrhythmia analysis. This beat-by-beat classification formed the framework of the second stage algorithm development in which beats segregated by type allowed selective averaging of normal beats prior to ST segment measurement. Automatic template generation created a reference normal QRS complex which was used in the subsequent waveform classification.

The first 20 beats of each passage were used to generate the template for the processing of the electrocardiogram. The dominant RR interval group G_d was determined from these 20 beats. After recognition of G_d, all beats associated with the dominant RR were signal-averaged to produce the initial template. The window size of the signal-averaged beat is determined automatically so that the template contains the correct portion of the P-QRS-T complexes. The following features were measured on the template: the P-Q segment level (baseline), and the QRS window size. The baseline measurement on the template is used for subsequent baseline correction prior to QRS waveform analysis, and the window size is applied to all QRS complexes for later calculations.

For waveform analysis, each QRS complex in the passage was subjected to a statistical comparison with the template. After baseline normalization, a correlation coefficient was computed to give an index representing normal or abnormal morphology.

A threshold applied to the correlation result separates QRS waveforms into one of two classes, normal and abnormal. This classification of each beat is combined with the corresponding RR interval to further classify each beat into one of eight classes: (1 = normal, 2 = premature ventricular beat, 3 = premature atrial beat, 4 = nonconducted beat, 5 = ventricular escape beat, 6 = long RR interval beat, 7 = compensatory pause, and 8 = aberrant beat). The normalcy of each RR is determined by comparing its interval to the running average RR denoted by RR_a, which is updated with each normal beat.

Automatic updating of the normal RR interval is done continuously during the entire ECG passage. This running RR is the average of the previous 16 normal RR intervals. Each beat is diagnosed in real time, a single beat diagnosis is computed and a contextual diagnosis is given when an arrhythmia is present.

Further analysis of the ECG is done for diagnosis of coronary artery disease (CAD) by recognition of ST segment changes which occur during exercise. The system implements a signal averaging technique which selectively includes only normal beats and rejects any that are not. The signal-averaging algorithm uses the single beat classification as its basis and allows inclusion of only beats with a code of 1 (normal) and accumulates 16 such beats into an averaged beat. The ST measurements are made on this averaged beat and this is repeated with each successive averaged beat of 16 normals. Quantities measured are ST depression and elevation, and ST slope. The location for the ST measurements (ST-point) varies with heart rate. The ST level is the difference in amplitude between the ST-point and the isoelectric level of the P-Q segment. The slope is determined from a window of five data points centered on the ST-point.

RESULTS

All passages of computer processed data were submitted to a cardiologist for evaluation. The cardiologist examined raw ECG data and correlated measurements with computer results. Arrhythmia analysis by computer was correct in 98.4% of all beat in abnormal rhythm passages, and 99.4% of all passages. In the exercise passages, the cardiologist and computer were in agreement (within 0.05 mV difference) in 46 of 48 ST level measurements (95.8%) from exemplary sets of averaged beats selected from the overall passages. Agreement in ST slope measurements was 91.7%. The cardiologist repeated his measurements on the digitized data reproduced by D/A converter. On these measurements the cardiologist and computer were in agreement in 97.9% of ST level measurements and 89.6% of ST slope measurements.

This work was supported by Elscint, Ltd., Haifa, Israel.

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Pour le titre du livre voir en seconde page.

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